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SHORT REPORT

The diagnostic challenge of pandemic H1N1 2009 virus in a dengue-endemic region: A case report of combined infection in Jeddah, Kingdom of Saudi Arabia

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Summary It is difficult to distinguish dengue fever from other febrile illnesses in a dengue-endemic area. This issue was compounded during the H1N1 2009 pandemic of influenza, which also presents as a febrile illness. This first laboratory-confirmed case of co-infection with dengue and influenza A H1N1 2009 strain in Jeddah, Saudi Arabia, highlights the importance of considering co-infections because not only is influenza an ongoing concern in Jeddah, but several viral hemorrhagic fever viruses circulate in this region.

Introduction

Dengue fever, the most common mosquito borne disease, is caused by one of the four serotypes of the dengue virus [1]. These viruses are a major international public health problem [2], infecting 50—100 million people worldwide annually, with approximately 12,500—25,000 deaths [3—5]. Dengue-infected patients present with a flu-like illness with a myriad of clinical features; infants and young children may have a fever with rash, whereas older children and adults may have either a mild fever or the classical disease with high fever, severe headache, pain behind the eyes, muscle and joint pains, and rash. Potentially serious complications of dengue fever, including dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), can develop [2,6].

Influenza is a serious public health problem that is characterized by a sudden onset of high fever,

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cough, headache, muscle and joint pain, severe malaise, sore throat and a runny nose. Influenza viruses circulate in every part of the world and annually cause epidemics during the autumn and winter in temperate regions; in some tropical countries, influenza viruses circulate throughout the year, with one or two peaks during the rainy seasons. Worldwide, these annual epidemics result in approximately 3—5 million cases of severe illness and approximately 250,000—500,000 deaths [7].

April 2009 marked the emergence of a novel influenza A H1N1 virus infection in the USA [8]. After spreading throughout the USA and Canada [9,10] the virus spread globally, and by 11th June, the WHO declared a phase 6 pandemic [11]. The first case of H1N1 in Saudi Arabia emerged in early June, and since then, the H1N1 has spread throughout the country.

Concurrent outbreaks of influenza and dengue fever have been reported in various tropical countries and territories, including Burma [12], India [13], Thailand [14] and Puerto Rico [15], leading to the delayed recognition of the presence of one or the other disease in the community. Both dengue fever and influenza have a wide range of clinical presentations with many overlapping features, and this overlap hinders the differentiation of the two diseases.

In this report, we discuss the diagnostic challenge with regard to the clinical profile of a case of laboratory-confirmed co-infection with dengue virus and pandemic H1N1 with persistent viral shedding.

Clinical profile

A 44-year-old info-tech worker presented to a tertiary care hospital in Jeddah with complaints of productive cough and fever for 2 weeks. At the time of admission to the hospital, the patient's temperature was 40 °C, and his blood pressure was 120/91 mmHg; he complained of headache, myalgia, chills, sore throat, nausea and anorexia. The patient also had a previous history of asthma. The chest examinations revealed disperse rhonchi, especially in the lower left and right mid zones. A chest X-ray showed bilateral basal patches of diminished aeration associated with bilaterally accentuated bronchovascular markings. Laboratory studies revealed the following: a leucocyte count of 4.8×10^9/L with predominant neutrophils (80.6%); a hematocrit of 40.1%; a platelet count of 163×10^9/L; creatinine, 98 μmol/L; albumin, 27.4 g/L; AST, 599 U/L; and ALT, 374 U/L. Respiratory and blood samples were collected and sent to the Jeddah Regional Laboratory for viral studies.

The patient was preliminarily diagnosed with community-acquired pneumonia and was put on 400 mg I/V Avelox (moxifloxacin) and nebulization. The various drugs used for nebulization during the course of the patient's illness were as follows: 2.5 mg/2.5 ml ampoules Ventolin (salbutamol) every 4 h, 500 μg/inhalation solution vial Atrovent (ipratropium inhalation) every 4 h and 1 mg/2 ml suspension Pulmicort (budesonide inhalation). The patient was re-evaluated the next day and was prophylactically administered 75 mg oseltamivir BID for 5 days while awaiting laboratory results. On day 3, the patient developed shortness of breath with tachycardia. The oxygen saturation fell to 83% with 5 liters of oxygen and repeat nebulization. The patient's temperature continued to spike to 39.8 °C with a respiratory rate of 35breaths/min and a pulse of 105 beats/min. On chest examination, air entry was decreased in the basal zones, and arterial blood gases revealed the following: a pO_2 of 53.9, a pCO_2 of 30.3 and a pH of 7.455. The ECG was normal. The patient developed hypoxic respiratory failure and was transferred to the intensive care unit (ICU), where he was treated for acute respiratory distress syndrome. Non-invasive mechanical ventilation was started. Bilevel positive airway pressure was provided with an initial inspiratory/expiratory positive airway pressure of 12/6 cm of water that was subsequently increased to 16/10 cm of water. Methylprednisolone was also added to the treatment regime. Gradually, the patient's condition improved on the day 6, and he was weaned off the mechanical ventilation after 8 days.

Laboratory results

The blood samples were sent to Jeddah Regional Laboratory, which is the reference virology laboratory that performs hemorrhagic fever panels for viruses that are prevalent or are likely to be introduced into the Kingdom. RT-PCR for dengue, West Nile, Alkhurma, Rift Valley, Crimean Congo and Chikungunya viruses (TIB MOLBIOL, GmbH, Germany) was carried out. Serotyping was performed using the Dengue LCD array 1.5 (Chipron, Gmbh, Berlin). The serology for dengue was performed using Panbio kits (Panbio Diagnostics, Brisbane, Australia). The nasopharyngeal swabs were tested for H1N1 using the Real Time ready RNA Virus Master & Real Time ready Influenza A/H1N1 Detection set (Roche). The NA gene of the influenza

virus was screened for the H275Y mutation which is responsible for oseltamivir resistance, with the Primer Design kit (UK).

Dengue RNA was detected in the blood samples, and serotyping revealed type 2 dengue virus. The serology for dengue was negative for IgM, IgG and NS1 antigens. The influenza A pandemic 2009 H1N1 strain was detected in the nasopharyngeal swabs. As the patient was in respiratory failure in the ICU, a repeat nasopharyngeal swab was sent to the laboratory after 7 days, and the influenza A pandemic H1N1 2009 strain was still detected. As the influenza virus persisted, the samples were screened for the H275Y mutation, but the isolated H1N1 strain was found to be the wild-type strain and not the mutant strain.

Discussion

Differentiating between dengue fever and influenza based on clinical features alone is difficult and requires laboratory confirmation. This patient presented with certain symptoms that are consistent with dengue fever, such as fever, myalgia, and sore throat, but certain features that are considered to be hallmarks of the disease, such as rash, retro-orbital pain, gastrointestinal symptoms, petechiae or bleeding, were not present. In addition, there was no thrombocytopenia, and the tourniquet test was negative. Therefore, it was difficult to distinguish dengue fever from influenza and other febrile illnesses.

The combination of dengue fever and influenza is usually not reported, although both present as febrile illnesses. The clinical syndrome of each disease is different: influenza-like illness and pneumonitis in pandemic influenza vs hemorrhagic manifestations in dengue fever. The management of the two diseases is also different: supportive therapy for dengue fever and oseltamivir for pandemic influenza. Clinically, the patient was diagnosed with community-acquired pneumonia and empirical antibiotic treatment was started, to which he did not respond. Oseltamivir was later added for influenza, but dengue was not the initial diagnosis.

Persistent viral shedding (PVS) has been defined as the detection of influenza A H1N1 virus by real-time PCR on day 7 after the initial diagnosis and has been associated with risk factors that include admission to the ICU, purulent expectoration, corticosteroid treatment and mechanical ventilation [16]. These factors were consistent with the findings of this patient. PVS has been demonstrated in hospitalized patients for both seasonal and pandemic influenza in 22—57% of patients 7 days after onset of illness [17,18]. The PVS, however, raised the suspicion that the pandemic H1N1 2009 strain was oseltamivir resistant; therefore, the samples were screened for the H275Y mutation. The strain turned out to be the wild-type strain and not the mutant oseltamivir-resistant strain with the H275Y mutation. The viability of the virus and its transmission after 7 days of illness has been described in a few studies [19].

Co-infection with dengue fever and H1N1 has been reported in tropical countries and territories, such as Nicaragua [20,21], Vietnam [22] and Puerto Rico [23], but the disease distribution in Jeddah, Saudi Arabia, is very different from that in other parts of the world. Jeddah is the gateway of entry into the Kingdom of Saudi Arabia for multiple nationalities throughout the year for the holy pilgrimage to Makkah and is also the point of entry for a multitude of pathogens carried by these visitors. This first laboratory-confirmed case of dengue fever and influenza A pandemic H1N1 2009 virus highlights the importance of considering co-infections, as such cases are a diagnostic challenge especially in Jeddah, Saudi Arabia, where several viral hemorrhagic fever viruses are suspected to circulate. It is not possible to distinguish these viral hemorrhagic fever viruses from each other or from other febrile illnesses based solely on the clinical features.

Conclusion

We report the first case of co-infection with Influenza A H1N1 and dengue fever in Saudi Arabia and describe the associated diagnostic challenges. We also demonstrated that our patient exhibited persistent viral shedding and suggest that further studies regarding the respiratory isolation of H1N1 be conducted. We also recommend that testing be performed for both viruses in regions where they co-circulate in population.

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